33. (Amended) A recombinant vaccinia virus of Claim 8, wherein the oncogene or proto-oncogene product [is] encodes a [protein] transmembrane tyrosine kinase, or an immunogenic portion thereof.

34. (Amended) A method of Claim 15, wherein the oncogene or proto-oncogene product [is] encodes a [protein] transmembrane tyrosine kinase, or an immunogenic portion thereof.

35. (Amended) A vector of Claim 29, wherein the oncogene or proto-oncogene product [is] encodes a [protein] transmembrane tyrosine kinase, or an immunogenic portion thereof.

Cancel Claims 24 and 26 which are directed toward non-elected subject matter.

REMARKS

Claim Amendments

Claims 1, 8, 23 and 27 have been amended to make clear that the oncogene or proto-oncogene of cellular origin induces an anti-tumor immune response in a host when expressed from a recombinant vaccinia vector.

Claims 10, 19 and 30 have been amended in order to make clear that Applicants' claims are directed toward immunogenic portions of the gene product.

Claims 24 and 26 have been cancelled as they are directed toward non-elected subject matter.

Claim 12 has been amended to delete the language, "an altered", which was deemed vague and indefinite.

Claims 15 and 22 have been amended to make clear that Applicants' claims are directed toward a virus which expresses an oncogene or proto-oncogene, rather than a virus which is merely capable of such expression.

Claim 22 has been further amended to make clear that the dose of administration is an effective amount.

Claims 32-35 have been amended to make clear that the protein kinase is a transmembrane tyrosine kinase. Support for this amendment appears on page 25, lines 9-13 of the specification.

Rejection Under 35 U.S.C. 101

Claims 15-22 and 34 have been rejected under 35 U.S.C. 101. The grounds, as set forth in the Office Action dated January 2, 1990, are that "it is unclear from the study of Lathe et al. that the expression of genes encoding TSA or the recombinant virus, per se, resulted in the elimination of tumors". However, Lathe et al. clearly show in Table 1 that animals infected with a vaccinia recombinant lacking polyoma sequences failed to reject tumors. Therefore, it is clear that the expression of genes encoding TSA resulted in the elimination of tumors, and not merely the recombinant virus per se.

A second reason is also provided in support of the new rejection. The rejection states that:

> . . . it is noted that the instantly claimed gene is of a cellular origin, not viral as described by Lathe and pointed out by Applicant. Applicant has failed to present any evidence on the instant record that the claimed method has utility. Applicants' reliance upon the method of use of inoculation of viral gene

> products to support the utility of a method of use of inoculation of cellular gene products is not considered persuasive, because Applicants' have failed to present any data or other supportive evidence that the inoculation of the recombinant virus bearing cellular genes will result in expression intracellularly and in sufficient amounts to produce the instantly claimed result.

This rejection is respectfully traversed. Applicants demonstrate in the Exemplification that mice infected with the recombinant vaccinia construct pEVAC-neu produce a high titre of antibody specifically reactive with the cellular gene product encoded by the recombinant virus. Furthermore, mice producing such antibodies were shown to be resistant to the outgrowth of p185-expressing tumor cells. Given this teaching, one of ordinary skill in the art would expect that the vaccination of a tumor-afflicted individual with a vaccinia virus carrying a tumor associated antigen of cellular origin would result in tumor regression. Therefore, both the originally and the newly asserted rejections under 35 U.S.C. 101 are unfounded and it is respectfully requested that they be withdrawn. Utility has been clearly established in the subject application.

Rejection Under 35 U.S.C. 112, First Paragraph

With the exception of the issues specifically discussed below in this section, each of the issues raised by the Examiner under 35 U.S.C. 112 have been addressed by the amendments specified above.

The specification has been objected to under 35 U.S.C. 112 as failing to provide an enabling disclosure

because Applicants did not provide in the specification "the complete chemical structure or the complete nucleotide sequence of the biological material ... that is essential for practicing the claimed invention." However, it is sufficient if a statement is made by Applicant, Applicants's Attorney of record, or Assignee's representative that a deposit has been accepted under the Budapest Treaty under conditions that all restriction upon the availability to the public of the deposit will be irrevocably removed upon the granting of the patent.

Accordingly, I, Giulio A. DeConti, Jr., declare and state that:

1. On September 1, 1987, a viable bacterial culture containing the plasmid pEVAC-neu was received by the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852.

2. During the pendency of the application, access to the deposit will be afforded to the Commissioner upon request.

3. All restrictions upon the availability to the public of the deposited material will be irrevocably removed upon granting of a patent on this application.

4. Each deposit will be maintained in a public depository for a period of at least 30 years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the biological material, whichever is longest.

On page 5, first full paragraph of the January 2 Office Action, the specification is objected to under 35 U.S.C. 112, first paragraph. In response to this rejection, Claims 32-35 have been amended to make clear that the protein kinase is a transmembrane tyrosine kinase. Several representatives of the transmembrane tyrosine kinase gene family have been cloned, and as pointed out in Amendment A, the members of this class have a highly conserved amino acid sequence. Each of the genes listed in the Markush grouping of Claims 10, 19 and 30 are members of the transmembrane tyrosine kinase class. This class of proteins is characterized by an extracellular binding domain, a membrane-spanning segment and an intracellular domain possessing the kinase activity. In light of Applicants' teaching, one of skill in the art, using no more than routine experimentation, could insert any of the genes belonging to this class into vaccinia virus and expect to obtain expression of the gene. This expectation stems from the highly conserved nature of this gene family. Furthermore, one skilled in the art, familiar with Applicants' teaching, would expect that an individual innoculated with a virus expressing such a cellular gene would induce a neutralizing immune response directed toward the gene product by the individual.

Applicant's are entitled to protection of the invention in its full breadth which extends beyond the transmembrane tyrosine kinase class. Applicants have enabled the method of immunizing described in the specification using any immunogenic oncogene or proto-oncogene of cellular origin which is associated with a tumor in an

individual. The only essential features of the encoded antigen is that it be of cellular origin and capable of stimulating an anti-tumor immune response. Many genes belonging to the class of oncogenes or proto-oncogenes of cellular origin have been cloned and the similarities between the members of this class, given Applicants' teaching, would lead to an expectation of success in expressing an oncogene or proto-oncogene product capable of inducing an anti-tumor immune response in a host.

Rejection Under 35 U.S.C. 112, Second Paragraph

Claims 1-3, 5-10, 12-13, 15-23, 27 and 29-25 have been amended to obviate the rejections based on 35 U.S.C. 112, second paragraph. Those rejections which are not obviated by amendment are discussed below.

Claim 1 et seq. have been rejected as vague and indefinite "because it is unclear what characteristics or properties separate a gene isolated from a cell's genome from that isolated from a viral genome, particularly when viral genes originated from the cellular genome." In the arguments which follow, in particular those presented in response to the §103 rejections, Applicants present in detail the distinction between true viral oncogenes (i.e. oncogenes carried by DNA tumor viruses) on the one hand, and oncogenes or proto-oncogenes of cellular origin (i.e. cellular proto-oncogenes or oncogenes carried by RNA tumor viruses). The elaboration presented herein obviates the §112, second paragraph rejection.

Claim 3 et seq. have been rejected as vague and indefinite because the recitation "of human origin" is

said to be unclear because it is unclear how one would identify genes of human origin from those of other origin given the sequence homology. Applicants submit that a gene of human origin is a gene isolatable from a human cell.

The recited limitation "potentially responsible" indicates that the proto-oncogene can become oncogenic. It is well known, for example, that a single amino acid change can be sufficient to convert a proto-oncogene into an oncogene. Therefore, even though the oncogenic potential of a proto-oncogene may not be manifested in the gene product, the gene product has utility in Applicant's invention.

Rejection Under 35 U.S.C. 102 and 103

Claims 1-23, 27 and 29-35 have been rejected under 35 U.S.C. 102(a) as anticipated by, or in the alternative, under 35 U.S.C. 103 as obvious over Lathe et al. In particular, the rejection states:

> The instant claims stand rejected for the reasons of record as stated at page 12, of the last Office Action. Applicant traverses the rejection on the grounds that allegedly the gene of Lathe is of viral origin whereas that instantly claimed is of human origin (emphasis added by Applicant).

The Examiner's statement of the distinction made by Applicants is incorrect. On page 16, lines 18-20 of Amendment A, Applicants clearly state that "Lathe et al. expressed viral encoded proteins in an immunized animal whereas Applicants expressed proteins encoded by cellular genes." In addition, the claims were amended to limit

their scope to oncogenes or proto-oncogenes of cellular origin. The proper distinction, therefore, is viral genes not of cellular origin (Lathe et al.) versus genes of cellular origin (Applicants).

With regard to the Examiner's comment that Lathe et al. "allegedly" describe work relating to a gene of viral origin (page 18, line 13), Applicants point out that Lathe et al. describe the expression of polyoma sequences in a recombinant vaccinia system. The polyoma viruses comprise one of the six major families of DNA tumor viruses. The DNA tumor virus oncogenes perform essential functions in the viral growth cycle and, as true viral genes, thay have no strict homologues or direct ancestors among the normal cellular genes of the host. Oncogenes carried by DNA tumor viruses, therefore, are not of cellular origin. Exhibit A has been attached to provide documentation on this point.

Cellular proto-oncogenes, and retroviral oncogenes (i.e. oncogenes carried by RNA tumor viruses) are of cellular origin. It is this class of genes to which Applicants claims are limited. Documentation as to the cellular origin of retroviral oncogenes is provided in Exhibit B. For example, on page 1067, lines 8-13, of Exhibit B, the authors state that:

> It now appears that retroviral oncogenes originate from normal genes of vertebrate cells (designated here by the generic term c-onc), that oncogenes and their vertebrate progenitors remain closely related if not identical, and that the functions of c-onc genes presage the effects of viral oncogenes in infected cells.

Thus, the discovery of c-onc genes has unveiled a family of cellular genes whose alteration or anomalous expression is responsible for oncogenic transformation. Applicants invention is clearly not anticipated by Lathe et al.

As to the obviousness rejection, the Office Action states:

> Alternatively, in view of the function of said gene (tyrosine kinase), it would have been obvious to choose and employ any tyrosine kinase gene in a manner as taught by Lathe, because it appears that the instantly claimed gene is a functional equivalent thereof, whose selection appears predicated upon its known and expected properties.

As to the suggestion that the viral gene described by Lathe is the equivalent to the oncogene or proto-oncogene of cellular origin as described in the subject application, Applicants re-emphasize that the viral oncogenes carried by DNA tumor viruses (Lathe et al.) have no homologue or counterpart in the cellular genome.

Furthermore, there are numerous examples which show it is not possible to predict, a priori, whether a particular gene can be expressed in vaccinia. For example, Li et al. (J. Virol. 62:776-782 (1988)) report that the vesicular stomatitis virus (VSV) M-gene could not be expressed in vaccinia virus, although other proteins from VSV were expressible. In another paper, Turner et al. (Virology 173:509-521 (1989)) report their

inability to express polio virus 2A gene in the vaccinia system. In yet another case, Fuerst et al. (Mol. Cell Biol. 7:2538-2544 (1987)) report low viability of vaccinia recombinants carrying as an insert, a T7 RNA polymerase gene, a target gene of interest and a T7 promoter.

In addition to the fact that expression in vaccinia is generally an unpredictable undertaking, the issue of immunogenicity in the host cell adds another layer of analysis. It is well known that even if a protein is expressed in vaccinia, it may not stimulate an immunogenic response in the host animal. For example, Gillespie et al. (J. Clin. Microbiol. 23:283-288 (1986)) report that no antibody to hepatitis B virus surface antigen was elicited in calves after repeated inoculation with vaccinia recombinants known to express the surface antigen. These same recombinants had been shown to elicit antibodies to the antigen in rabbits. Martin et al. (J. Virol. 61:726-734 (1987)) report that vaccinia recombinants carrying the herpes simplex type 1 gene encoding glycoprotein D were able to stimulate some HSV-specific T cell responses but did not induce cytotoxic T cells.

Furthermore, although an antigen may be immunogenic, it will not necessarily stimulate a neutralizing immune response. For example, Morgan et al. report that several vaccinia recombinants carrying EBV gp340 inserts, which were shown to be immunogenic in that antibodies were produced to the EBV encoded product, did not protect animals challenged with a tumorigenic dose of the virus.

In connection with the obviousness rejection, the Office Action also states, on page 11, lines 15-20:

> First, the claims fail to recite the exclusive limitation that no viral (i.e. immunogenic) polypeptide portions are expressed with the cellular gene product. Second, other cellular gene products are known in the art that are immunogenic when expressed in a context other than the native environs.

This rejection is unclear. As to the first point, it is undoubtedly true that vaccinia gene products are expressed, along with the oncogene or proto-oncogene of cellular origin, from the recombinant construct described by Applicants. Furthermore, the majority of these vaccinia encoded proteins are probably immunogenic. However, it is the oncogene or proto-oncogene product which is responsible for the immune response directed against the tumor, and not the vaccinia encoded products.

As to the second point, Applicants repeat that it is not possible to predict, a priori, whether or not a particular gene is expressible in vaccinia. Furthermore, whether an expressed immunogen will stimulate an immune response, and whether the immune response will be protective, are also impossible to predict.

Claims 1-23, 27 and 29-35 have been rejected under 35 U.S.C. 103 as being unpatentable over Kornbluth or Mansour in view of Davis and Paoletti. The arguments presented above in connection with the other §103 rejections apply with equal weight to these references. Even in light of the combined teachings of these references, it would have been non-obvious to one skilled

in the art that an oncogene or proto-oncogene of cellular origin could stimulate a protective immune response when expressed in a vaccinia system.

The rejection under §103 continues on page 12, lines 8-20:

> Applicant has failed to limit the claims to the expression of polypeptides of only cellular origin. Even assuming arguendo that the claims were so limited, it is pointed out that immunogenicity is a complex property. The simplistic allegation that viral gene products are expected to be immunogenic whereas cellular gene products are not, fails to address the environs of expression, the purity or associations of the expressed gene product or host in which said genes are expressed.

It is unclear to Applicants what is meant by the first sentence of the above-quoted rejection. Each of the independent claims under consideration is limited in scope to an oncogene or proto-oncogene <u>of cellular origin</u>.

As to the complex nature of gene expression, Applicants agree with the assertion that immunogenicity is a complex property. Furthermore, as pointed out above, simply because a particular protein stimulates an immune response, it does not necessarily follow that the response will be a neutralizing response. However, Applicants have identified a highly conserved class of proteins, one member of which does stimulate such a response. Given the structural similarity of the proteins, one skilled in the art would predict that the other members of the oncogene class, and especially the transmembrane tyrosine kinase class, would stimulate a similar response.

SUMMARY

For the foregoing reasons, Applicants request that the Examiner reconsider the application. If the Examiner believes that a telephone conversation will expedite prosecution of this application, the Examiner is urged to call Applicants' Attorney at (617) 861-6240.

Respectfully submitted,

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